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Authors
Alizadeh, Reza
Vickers, Laura
Hirunpatravong, Pradtana
et al.

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A Phenotype of Primary Open-angle Glaucoma With Systemic Vasospasm

Reza Alizadeh, MD, Laura Vickers, MD,* Pradtana Hirunpatravong, MD,* Pablo Romero, MD,* Mark C. Lin, MD,* Farideh Sharifipour, MD,† and Joseph Caprioli, MD**

Purpose: Primary open-angle glaucoma (POAG) patients constitute a heterogenous group. Identification of phenotypic subtypes among these patients may provide a deeper understanding of the disease and aid associations with genotypes. We describe a phenotype of POAG patients associated with a constellation of systemic disorders; patients with this phenotype seem to be vulnerable to optic nerve damage at low intraocular pressures.

Materials and Methods: In this retrospective study, we evaluated the medical records of active Jules Stein Eye Institute glaucoma patients from January 1996 to 2017 and included subjects with POAG, acquired pits of the optic nerve (APON), and at least one of the following: systolic blood pressure persistently ≤ 100 mm Hg, history of migraine headaches or migraine variant, and the Raynaud syndrome.

Results: Of 87 patients (125 eyes) with APON, 37 patients (55 eyes) met the study criteria. In total, 34 patients were female (92%). The median age at the time of diagnosis was 55 years. Nineteen patients (73%) had low systolic blood pressures, same number had Raynaud syndrome, and 25 (68%) had a history of migraine.

Conclusions: We describe a POAG subtype with APON and systemic vascular instability, predominantly female in their sixth decade of life who demonstrate progressive glaucomatous visual field damage at low intraocular pressure. We suggest that this clinical picture represents an important phenotype of POAG, and that identification and further study of it will help guide diagnosis and development of individualized treatments.

Key Words: vasospasm, primary open-angle glaucoma, migraine headache, Raynaud disease, low systemic blood pressure, acquired pits of the optic nerve

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Various patterns of glaucomatous optic nerve damage have been identified which may correspond to different patterns of visual field loss.[1,2] As the development and application of genome-wide association studies (GWAS), we are learning more about the heterogeneity of glaucoma as a disease.[3] Many genes and single nucleotide polymorphisms have been discovered in association with primary open-angle glaucoma (POAG). However, beneficial clinical applications of these discoveries is hampered by our poor ability to sufficiently phenotype different subsets of patients with POAG. Establishing the association of various single nucleotide polymorphisms and genes with their respective phenotypic variants of POAG, if any, may allow us to target our monitoring and treatment algorithms for certain groups of patients; this will require the definition of identifiable clinical phenotypes.[3,4] In addition, identifying phenotypic subclasses of glaucomatous optic nerve damage can be helpful in aiding clinicians in diagnosis and treatment.[5]

One distinct pattern of optic nerve damage with corresponding visual field loss is the acquired pits of the optic nerve (APON). APON was first described in 1977 as a focal loss of neural tissue associated with pronounced excavation and loss of normal architecture of the lamina cribrosa.[6,7] Radius et al[8] reported the first cases of APON in glaucoma patients, whereas Spaeth[9] and Javitt et al[10] confirmed and further described the presence of this type of optic nerve damage in glaucoma. APON is more frequently observed in patients with what has been described as normal tension glaucoma (NTG).[11,12] The associated visual field loss tends to be deep, with sharply delineated scotomata near and sometimes involving fixation.[6,7,11–13] APON has also been shown to be a risk factor for rapid visual field loss.[12]

This case series describes a subgroup of POAG patients who have APON and risk factors for systemic vascular instability including migraine headache, Raynaud phenomenon, and low blood pressure (BP). We propose that this group represents a phenotypic subtype of POAG in which signs and symptoms of vasospasm are associated findings, and which may contribute to their optic nerve vulnerability.

MATERIALS AND METHODS

The study protocol was approved by the Institutional Review Board at the University of California Los Angeles (UCLA), and all study procedures adhered to the recommendations of the Declaration of Helsinki and conformed to HIPAA policy. All charts of POAG patients examined in the Glaucoma Division of the Stein Eye Institute, UCLA, Los Angeles, California, from January 1996 to 2016 and who have had a visit within 12 months of the start of data collection (total of 2547 charts) were reviewed. Those with acceptable quality optic nerve stereoscopic photographs, which includes nearly 1000 imaging, were screened for the presence of APON by an experienced glaucoma specialist (J.C.) by examination of the

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From the *Glaucoma Division, Jules Stein Eye Institute, University of California Los Angeles (UCLA), Los Angeles, CA; and †Department of Ophthalmology, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
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Reprints: Joseph Caprioli, MD, Glaucoma Division, Jules Stein Eye Institute, David Geffen School of Medicine, University of California Los Angeles (UCLA), 100 Stein Plaza, Los Angeles, CA 90095 (e-mail: caprioli@jsei.ucla.edu).

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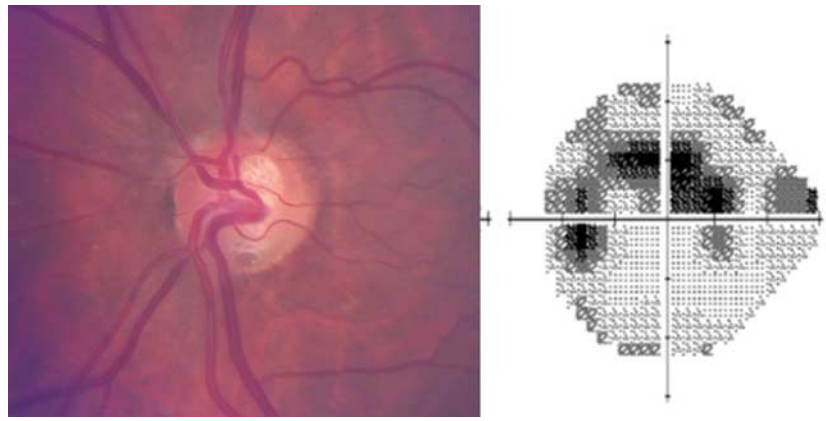

FIGURE 1. The standard stereoscopic optic disc photograph used to define APON with the pattern deviation plot from 30-2 visual field perimetry. An inferior APON is visible in this optic nerve with corresponding pronounced defect within 5 degrees of fixation. APON indicates acquired pits of the optic nerve.

photographs. The criteria for the presence of APON were similar to previously published descriptions.[10–12]

(1) A sharply localized depression or absence of visible lamina cribrosa, with deep excavation and loss of normal laminar architecture, located at the inferotemporal or superotemporal pole of the optic disc, and distinct from the appearance of the classic congenital pit of the optic nerve.
(2) Extension of the APON to the outer edge of the disc so that little or no rim tissue remained adjacent to the pit.
(3) No evidence of coloboma or subretinal fluid.

In addition to the above criteria, a reference stereoscopic optic disc photograph was used to define APON (Fig. 1). Three experienced, masked, independent observers then examined the stereoscopic photographs and confirmed or denied the presence and location of APON. The decision about the presence or absence of an APON was made by agreement of at least 2 observers (not including J.C.). Optical coherent tomography was not used to confirm the presence of APON. Patients with any ocular or intracranial disease affecting the optic disc or visual field were excluded (including but not limited to intracranial mass, central retinal vein/artery occlusion, branch retinal vein/artery occlusion, and pathologic myopia).

Patients included in this study had POAG and APON with any one of the following: systolic BP persistently <100 mm Hg without medication, a history of migraine or migraine variant headache, and symptoms of Raynaud syndrome or phenomenon. Patients were screened for these underlying medical conditions by self-reported history. To avoid recall bias, only patients with confirmed diagnosis by physician were included and patients with only self-reported problems were excluded. Medical records were reviewed and the following information was recorded: ethnicity, systemic conditions and medications, APON location and laterality, age at the time of diagnosis, family history of glaucoma, sex, history of intraocular surgery, spherical equivalent and refractive error, central corneal thickness, and presence of peripapillary atrophy. Best-corrected visual acuity, number of glaucoma medications, and intraocular pressure (IOP) were recorded at each visit. All patients with documented untreated IOP never higher than 21 mm Hg were considered as NTG.

All visual fields were obtained with the Humphrey Field Analyzer 630 (Program 30-2 or 24-2, SITA Standard algorithm; Humphrey Instruments Inc., San Leandro, CA). An acceptably reliable visual field defect was defined as one with <30% false-positive responses, false-negative responses, and fixation losses. Typical glaucomatous visual field defects were defined in 2 consecutive, reliably performed, baseline automated threshold field tests as having an abnormal Glaucoma Hemifield test or pattern SD and at least 1 of the following 3 criteria: ≥ 2 adjacent points with $P < 0.01$ or greater loss in the superior arcuate or inferior arcuate zones, compared with perimeter-defined age-matched normal values; ≥ 3 adjacent points with $P < 0.05$ or greater loss in the superior arcuate or inferior arcuate zones; or a 10 dB difference across the nasal horizontal midline in ≥ 2 adjacent locations (Fig. 1).

RESULTS

Of 87 patients (125 eyes) with APON, 37 patients (55 eyes) met the study criteria. The expert panel did not agree on 25 eyes with APON and they were excluded from study.

In total, 37 patients (55 eyes) met the inclusion criteria for this series (Table 1) with a median follow-up of 10.8 years (range, 0.9 to 31.7 y). In total, 34 patients (92%) were female, and median age at diagnosis of POAG was 55.1 years (range, 19.9 to 79.3 y) (Fig. 2). Median treated IOP during the follow-up period was 13 mm Hg (range, 7 to 40 mm Hg) (Fig. 3). The mean ($\pm$ SD) number of glaucoma medications used was 1.3 ± 1.2. A visual field defect within 10 degrees of fixation was observed in 44 eyes (80%). In 48 eyes (87%), the APON was located inferiorly, and bilateral APON was noted in 18 patients (49%). Low BP and Raynaud disease had the same incident and were found in 19 patients (73%), whereas history of migraine headache or migraine variant had a lower incident and was present in 25 patients (68%). Baseline mean deviation (MD) and visual field index (VFI) was -5.55 ± 6.10 dB and $84.2\% \pm 18.2\%$, respectively. In total, 42 patients had at least 1 year of follow-up and at least 6 reliable visual fields to calculate the rate of MD and VFI change. In this group of patients, rate of MD change was -0.33 ± 0.7 dB/year ($P < 0.001$) and VFI was $-1.0\% \pm 2.0\%$/year ($P < 0.001$). Examples of the optic nerve appearance with the corresponding visual fields can be seen in Figure 4.

Among the 37 patients in this series, a subgroup of 21 patients (57%) had ≥ 2 systemic risk factors for vasospasm.

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TABLE 1. Demographic Characteristic for Patients With Primary Open-angle Glaucoma, Vasospastic Type

	At Least 1 Systemic Vasospastic Condition	≥2 Vasospastic Conditions
No. patients	37	21
No. eyes	55	30
Age (y)	53.2 ± 14.4	54.1 ± 10.9
Sex		
Female	34 (92)	8 (100)
Male	3 (8)	0 (0)
Race		
Caucasian	17 (46)	10 (48)
Other	20 (54)	11 (52)
Right/left eye	27/28	15/15
Low systolic blood pressure	16 (72.7)	17 (81)
Raynaud disease	19 (51)	16 (76)
History of migraine or migraine variant headache	25 (68)	16 (76)
All IOP < 21 mm Hg	30 (54.5)	30 (100)
Mean IOP	13.5 ± 4.7	12.6 ± 3.6
No. medication	1.3 ± 1.2	1.3 ± 1.1
Inferior APON	48 (87)	24 (80)
Bilaterality	18 (48.6)	9 (30)
Central corneal thickness (μm)	553 ± 40	545 ± 39.2
Visual acuity (logMAR)	0.1 ± 0.6	0.06 ± 0.04
Glaucoma surgery	20 (36)	8 (26)
Topical beta blocker usage	35 (64)	16 (53)
Spherical equivalent	−3.9 ± 0.6	−4.1 ± 0.5

There are no statistically significant difference between groups, except for sex, which females were significantly higher when there are ≥2 vasospastic conditions. Spherical equivalent is calculated as sphere+cylinder/2.

Data presented as mean ± SD and n (%).

APON indicates acquired optic nerve pit; IOP, intraocular pressure; logMAR, logarithm of minimum angle of resolution; mm Hg, treated or nontreated: millimeters of mercury.

Within this cohort, all patients were female and the median IOP during the follow-up time was 12 mm Hg (range, 1 to 30 mm Hg). Median age in this subgroup was 53.8 years (range, 26.6 to 69.1 y), and median duration of follow-up was 10.8 years (range, 0.9 to 21.4 y). In 28 eyes (93%) of this subgroup, a scotoma within 10 degrees of fixation was present. Bilateral APON was observed in 21 patients (30%).

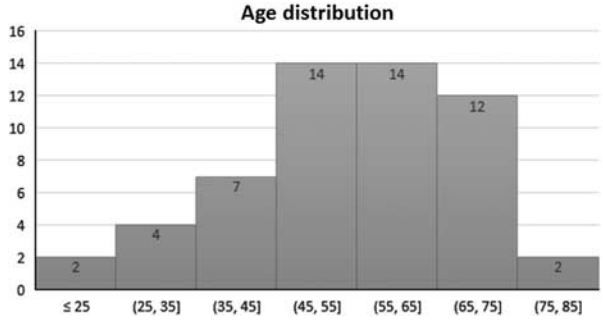

FIGURE 2. Bar graph of age distribution in patients with vasospastic subtype of primary open-angle glaucoma. The number on the top of each bar represents number of patients and the range for each bin is depicted below each bar.

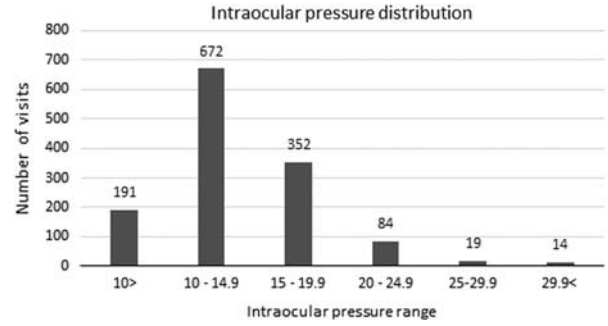

FIGURE 3. Bar graph of intraocular pressure distribution in patients with vasospastic subtype of primary open-angle glaucoma in each visit. The number on the top of each bar represents number of visits and the range for each bin is depicted below each bar.

Seventeen patients in this subgroup had been diagnosed with low BP (81% of this subgroup); the remaining 4 patients were the only patients in the entire series with a history of smoking. Migraine headache and Raynaud syndrome were present in 16 patients (76%).

DISCUSSION

To help develop clinical innovations based on genome-wide association studies, genetic findings should be associated with phenotypic subclasses of glaucoma patients. A comprehensive subgroup analysis of clinical glaucoma subtypes is therefore an important step,[3,4] and is not feasible unless distinct phenotypes of glaucoma, even though differences may be subtle, are first more elaborately defined. We believe the description of a phenotype we term as "POAG, vasospastic subtype" can forward this goal, and also help clinicians in guiding the best, individualized treatment options.

The APON is a distinct structural variant of optic nerve damage, defined as a deep, localized excavation of neural rim with localized depression and loss of normal laminar architecture of the lamina cribrosa. The affected area is pale and has little or no rim tissue remaining adjacent to the disc edge.[9,10] APON has been identified as a risk factor for rapid progression of visual field loss,[11–15] and perimetric and optical coherent tomography studies[14,16] have shown that this loss is focal and corresponds to the location of the APON.[15] It is postulated that some APONs may represent laminar disinsertions from the peripapillary scleral infrastructure and that clinically obscured laminar disinsertions may be a precursor to APON.[17] Laminar disinsertions occurs twice as frequently in eyes with optic disc hemorrhage[18] and is a risk factor for glaucomatous visual field progression.[19]

In this series, we describe 37 patients with APON, mostly female and middle-aged with at least 1 systemic manifestation of vasospasm (low systemic BP, migraine, or Raynaud phenomenon). Although low systemic BP is not always a manifestation of vasospasm, none of these patients had a history of iatrogenically low BP from overtreatment, or from known autonomic vascular dysregulation. In the subgroup with at least ≥2 systemic vasospastic risk factors, all patients were female and had low IOPs. Previous studies have well described this vasospastic type of NTG and have showed similarly that systemic vasospastic conditions such as migraine headache and Raynaud phenomena are more prevalent in NTG patients.[10,12,20–22]

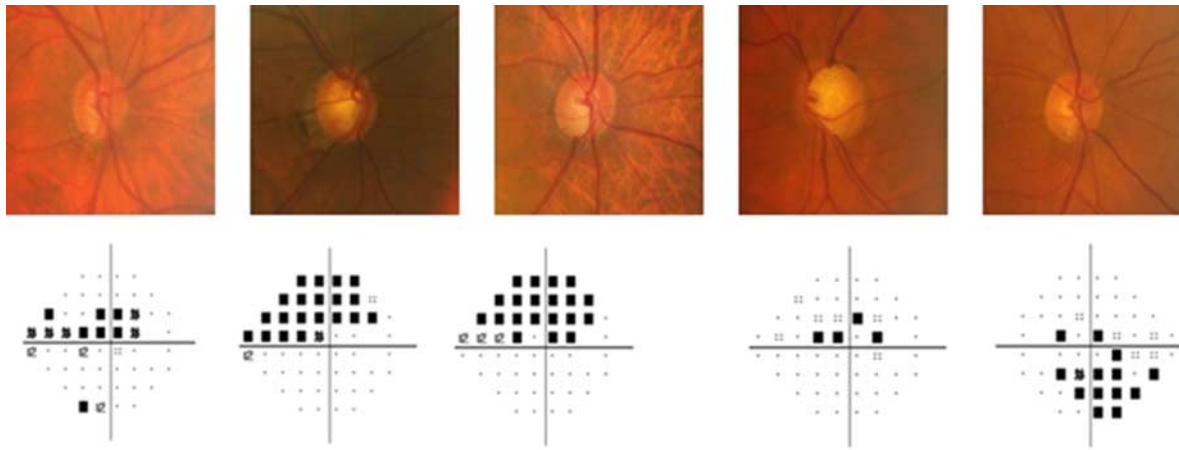

FIGURE 4. Examples of the optic nerve with the corresponding visual field. There is a spectrum of visual field defects depending on the site of the acquired pits of the optic nerve.

APON was recognized most frequently at the inferior pole of the optic nerve in our patients (87%), which is higher compared with previous studies (ranged between 70% and 80%).[9,10,12,14] It has been suggested that lower pressure POAG patients (identified by some as NTG) have thinner neuroretinal rims compared with higher pressure POAG controls, which is most marked in the inferior and inferotemporal optic disc regions.[9,11,12] It has been also shown that optic nerve cupping in glaucoma patients is deepest in the inferior aspect of the disc where the connective tissue bundles are thinnest and farthest apart.[11,23,24]

In this study, bilaterality of APON was found more frequently than in some previous reports (30% in patients with ≥ 2 vasospastic conditions and 48.6% in patients with 1, versus reports by Cashwell of 20.6% and Nduaguba of 16%)[12,14] and comparable to the Ugurlu et al report of 48%.[10] The longer follow-up in this case series may have allowed for observation of a higher rate of bilateral APON as progressive optic nerve damage occurred over time.

Our patients with APON had a higher female to male ratio than previous studies (all of our patients with at least 2 vasospastic conditions and 92% of patients with 1 condition were female).[11] It has previously been shown that NTG, migraine headaches, and Raynaud disease are more frequent in females.[10] There is also a higher association between these systemic conditions and lower pressure POAG[22] as compared with higher pressure POAG, which may be due to a common vascular pathology which underlie both diseases.

Patients in this series were significantly younger than patients with POAG who have APON reported in previous studies.[10,12] We postulate that underlying systemic vasospastic conditions play a role in optic nerve vulnerability to damage. Studies in animal models of optic nerve ischemia and glaucoma show that optic nerve ischemia causes demonstrable and localized damage of the optic nerve without IOP elevation.[25–27] Ocular perfusion pressure (OPP) is known to be related to systemic BP, and the relationship between systemic BP and glaucoma is well established.[25] In previous population-based studies it has been shown that lower BP and OPP are associated with glaucoma. The Barbados Eye Survey[28] showed that higher systolic and diastolic BP can be considered as protective factors for glaucoma, whereas individuals with lower OPP, especially diastolic OPP (< 55 mm Hg), have greater relative risk of having glaucoma (relative risk = 3.2). Another factor can be nocturnal BP dips; 24-hour BP monitoring has revealed nocturnal dips as a risk factor for accelerated progression of glaucoma. These dips can sometimes be iatrogenic, caused by overmedication of systemic hypertension.[29]

The Los Angeles Latino Eye Study[30] revealed that lower mean OPP was associated with higher risk of glaucoma in the population. Vigorous lowering of systemic BP with medication might have the same effect on OPP and have been shown to be associated with glaucoma,[31,32] especially if it is associated with nocturnal hypotension.[29,33] Low BP was seen in the majority of the patients in our study; patients who did not have a history of low systolic BP had a history of smoking. Smoking is suggested as a risk factor for optic nerve vulnerability as well, via the nitric oxide pathway, or other mechanisms.[34] Cigarette smoking can decrease the bioavailability of endothelium-derived factors and cause dysfunctional vasomotor responses.[35,36] Published data from clinical and animal studies have showed that vascular dysfunction induced by smoking is initiated by the reduced bioavailability of nitric oxide[35,37,38] with subsequent vasoconstriction, stimulation of adhesion of leukocytes to the endothelium and atherosclerosis.[39,40]

The relationship between systemic vascular structure and optic nerve blood flow has been shown in previous studies. A relationship between fingernail bed blood flow and optic nerve head flow, especially in glaucomatous patients, has been shown.[41,42] In addition, not only was the flow in nail beds an indicator of optic nerve head flow, but hemorrhages in nail beds were predictors of optic disc hemorrhages in glaucomatous patients, including NTG patients.[42–44]

The rate of MD change for this syndrome in our study was -0.33 ± 0.7 dB/year which is comparable to other POAG patients and is significantly higher than in normal eyes.[45,46] The fact that regardless of lower treated IOPs, the finding that the visual field worsens over time needs to be considered in choosing treating options in these patients, including surgery to achieve very low target pressures.

A limitation of the present study is the retrospective design, small number of patients, and selection bias.

Untreated levels of IOP were available for two third of the patients. Further prospective cohort studies of patients with systemic vasospasm would help to clarify the hypotheses we have laid out in this case series. The major goal of this study is to show that this phenotype exists, and can be described, despite the obvious limitations. As other studies suggest, phenotyping is necessary for better understanding the rapid development-related results of genomic technology.[47]

Of note, the expert panel did not examine all fundus photographs as it was found to be time-consuming. However, it seems that this would have increased the likelihood of this syndrome as there might be more APON patients who meet the inclusion criteria that have not been picked up by the initial screener, hence the incidence/prevalence rate could have been underestimated.

In addition, as Jules Stein is a referral institute, we do not have clean data about the baseline untreated IOP. As this would be mainly self-reported, which increases the risk of recall bias, these data were included in this study.

We have defined a phenotype, "POAG, vasospastic type" and propose that the predominant characteristics of this phenotype include focal optic nerve damage in the form of APON, POAG with progression at low IOP, middle-age (40 to 60 y), female sex, and associated findings of Raynaud phenomena, migraine, and low BP. We believe that these systemic associations are signs of a vasospastic vascular instability that predisposes the optic nerve to focal damage, manifested as APON. Patients in this subgroup show progressive, focal optic nerve damage at a young age, and identification of such patients may guide the clinician to pursue appropriately aggressive IOP-lowering and close monitoring.

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